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(54) Title: DOSAGE FORMS HAVING IMPROVED RELEASE PROPERTIES

(57) Abstract

The invention relates to tablets made by directly compressing a composition containing binary active agent/solubilizer microspheres. The microspheres are made via liquiflash processing.

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DOSAGE FORMS HAVING IMPROVED RELEASE PROPERTIES

Related Application

This application is a continuation-in-part of U.S. application Serial No. 08/946,065, filed October 7, 1997.

Field of the Invention

The invention relates to dosage forms containing pharmaceutically active agents and having superior *in vitro* and *in vivo* characteristics when compared to conventional products. The tablets contain thermoformed particulates containing active agents along with a variety of pharmaceutical additives, including optional coatings.

Background of the Invention

For several types of pharmaceutical products, *e.g.*, anticholesterolemics such as lovastatin, the attainment of a high C_{MAX} (highest plasma concentration at any point in time) and large A.U.C. (total amount of drug absorbed as measured by the area under the curve of a plot of plasma concentration vs. time) is desirable. However, the poor solubilities of lovastatin and other agents of its type make attainment of these goals problematic.

The invention deals with dosage forms which use binary particulates, preferably microspheres, containing only active agent(s) and solubilizing agent(s). The particulates are dry, solid dispersions made by subjecting the active and solubilizing ingredients to liquiflash conditions to directly produce microspheres or non-spherical particulates. When they contain certain amounts of solubilizing agents, the particulates are used in products that give higher C_{MAX} and A.U.C. values when ingested than products that do not contain the same types and amounts of solubilizers.

Melt blends of active agents with solubilizers such as surfactants have been previously disclosed.

U. S. Patent 4,944,949 discloses micelles of non-steroidal anti-inflammatory drugs (NSAIDS) with nonionic surfactants such as poloxamers (col. 5, line 31). Micelles are aggregates in which surfactant molecules are arranged in a spheroidal structure, with the hydrophobic regions at the core and the hydrophilic regions at the

other surfaces. Drug:surfactant ratios of 1:5.7 to 1:50 are disclosed at column 12, line 57.

U. S. Patent 5,281,420 shows tebufelone, an anti-inflammatory agent, in solid dispersions containing 15% to 75% tebufelone and 25% to 65% of a poloxamer surfactant (col. 1, lines 35-51).

U. S. Patent 5,525,353 deals with laxative compositions which contain poloxamer surfactants, as stool softeners, melt-blended with stimulants. The ratio of surfactant to stimulant is 2:1 to 20:1 (col. 2, line 22+). The compositions are administered in hard gelatin capsules.

EPO Application 0 317 780, published May 31, 1989, shows quick-release and sustained-release formulations containing dihydropyridine calcium channel blockers and poloxamer surfactants. The quick release compositions contain 0.15:1 to 0.5:1 of hydroxypropylmethylcellulose to dihydropyridine/poloxamer complex (p. 6, l. 48-49). The complex contains 1:1 to 1:10 ratios of drug to surfactant (page 6, lines 25-27).

In publications dated 1994 and 1997, BASF Corporation discloses melt extruded drug/polymer products. But details of their preparation are not disclosed.

WO97/02017, published January 23, 1997, discusses oral dosage forms which contain a solid dispersion of an active ingredient in a poloxamer polymer. The ratio of active agent to poloxamer is 0.1:1.0 to 10.0:1.0 (page 3, line 280.

U. S. Patent 4,727,109 shows liquid preparations containing an active agent and a carrier system consisting of a hydrophilic component, a hydrophobic component and a solubilizer. The hydrophilic component may be a polyethylene glycol or a polyoxyethylene/polyoxypropylene copolymerizate. See column 2, lines 35-44.

U. S. Patent 5,456,923 describes solid dispersions of drugs in polymers made by extruding the two together and pulverizing the extrudate. Polyoxyethylene/polyoxypropylene copolymers are disclosed at column 3, lines 33-34, as plasticizers.

U. S. Patent 5,292,461 deals with pellets produced by spraying an active agent with a wetting agent. Polyethylene glycols are disclosed as lubricants (column 7, line 62) and agents which influence the release of the active ingredient (column 8, lines 1-2).

Poloxamers are recited as surface-active agents (column 7, line 65).

The art has not successfully blended polymeric solubilizing agents with actives to directly produce stable, dry particulates, notably microspheres, of uniform size.

Summary of the Invention

The invention is concerned with particulates containing only active agents and solubilizers, and with dosage forms, e.g., capsules and tablets, made therefrom as well as with thermoforming processes for making these dosage forms.

Dosage forms of the invention can contain thermoformed particulates along with pharmaceutical additives. These dosage forms, such as caplets, capsules and tablets, are highly stable and give improved *in vitro* solubility/-dissolution and *in vivo* performance for the active agent(s) therein, relative to delivery of the same active agent(s) without the microspheres. Oral dosage forms are typical.

When spherical, the particulates of the invention are readily flowable, so that processing and delivery to the consumer are facilitated, regardless of the type of product in which they are used.

Detailed Description of the Invention

Unless otherwise stated, all percentages recited herein are weight percentages based on total composition weight.

The particulates of this invention are made by subjecting at least one active and at least one solubilizer to thermoforming techniques, e.g. liquiflash processing or extrusion.

Liquiflash and flash flow techniques for making microspheres are known in the art. One process uses the apparatus disclosed in U. S. Serial No. 08/874,215, filed June 13, 1997. The liquiflash process is also described in U. S. Patent 5,683,720. The disclosures of both are incorporated herein by reference.

U. S. Patents 5,445,769 and 5,458,823 show devices which can be used to make liquiflash microspheres. These disclosures are also incorporated herein by reference.

In addition, extrusion mixing can be used to make the particulates of the invention. In some preferred embodiments, the active ingredient(s) and polymeric

solubilizer(s) are combined in suitable ratios to yield eutectic mixtures or other drug/solubilizer mixtures.

Feedstocks

Particulates used in the invention are made from binary feedstocks which are either spheronized using liquiflash techniques or made into particulates using other thermoforming processes. The feedstocks contain, as the only ingredients:

(a) about 5% to about 80% of at least one active ingredient, and

(b) about 95% to about 20% of at least one polymeric solubilizing agent.

Drug/solubilizer combinations containing about 10% to about 95% active, and preferably 30% to about 90% active and most preferably about 40 to about 80% active are useful in making particulates in general. Combinations containing about 20% to 40% active agent and about 80% to 60% solubilizer are highly effective in making microspheres. Non-spherical particulates preferably contain drug:solubilizer ratios of about 60:40 to about 75:25. In some cases excess solubilizer is used, so that the active is enveloped or coated by the solubilizer.

The active ingredients useful herein can be selected from a large group of therapeutic agents. Respective classes include those in the following therapeutic categories: ace-inhibitors; alkaloids; antacids; analgesics; anabolic agents; anti-allergy agents; anti-anginal drugs; anti-arrhythmia agents; antiasthmatics; antibiotics; anticholesterolemics; anticonvulsants; anticoagulants; antidepressants; antidiarrheal preparations; anti-emetics; antihistamines; antihypertensives; anti-infectives; anti-inflammatories; antilipid agents; antimanics; anti-migraine agents; antinauseants; antipsychotics; antistroke agents; antithyroid preparations; anabolic drugs; antiobesity agents; antiparasitics; antipsychotics; antipyretics; antispasmodics; antithrombotics; antitumor agents; antitussives; antiulcer agents; anti-uricemic agents; anxiolytic agents; appetite stimulants; appetite suppressants; beta-blocking agents; bronchodilators; cardiovascular agents; cerebral dilators; chelating agents; cholecystekinin antagonists; chemotherapeutic agents; cognition activators; contraceptives; coronary dilators; cough suppressants; decongestants; deodorants; dermatological agents; diabetes agents; diuretics; emollients; enzymes; erythropoietic drugs; expectorants; fertility agents;

fungicides; gastrointestinal agents; growth regulators; hormone replacement agents; hyperglycemic agents; hypoglycemic agents; ion-exchange resins; laxatives; migraine treatments; mineral supplements; mucolytics, narcotics; neuroleptics; neuromuscular drugs; non-steroidal anti-inflammatories (NSAIDs); nutritional additives; peripheral vasodilators; polypeptides; prostaglandins; psychotropics; renin inhibitors; respiratory stimulants; sedatives; steroids; stimulants; sympatholytics; thyroid preparations; tranquilizers; uterine relaxants; vaginal preparations; vasoconstrictors; vasodilators; vertigo agents; vitamins; wound healing agents; and others.

Active agents which may be used in the invention include: acetaminophen; acetic acid; acetylsalicylic acid, including its buffered forms; acrivastine; albuterol and its sulfate; alcohol; alkaline phosphatase; allantoin; aloe; aluminum acetate, carbonate, chlorohydrate and hydroxide; alprozolam; amino acids; aminobenzoic acid; amoxicillin; ampicillin; amsacrine; amsalog; anethole; ascorbic acid; aspartame; astemizole; atenolol; azatidine and its maleate; bacitracin; balsam peru; BCNU (carmustine); beclomethasone diproprionate; benzocaine; benzoic acid; benzophenones; benzoyl peroxide; benzquinamide and its hydrochloride; bethanechol; biotin; bisacodyl; bismuth subsalicylate; bornyl acetate; bromopheniramine and its maleate; buspirone; caffeine; calamine; calcium carbonate, casinate and hydroxide; camphor; captopril; cascara sagrada; castor oil; cefaclor; cefadroxil; cephalexin; centrizine and its hydrochloride; cetyl alcohol; cetylpyridinium chloride; chelated minerals; chloramphenicol; chlorcyclizine hydrochloride; chlorhexidine gluconate; chloroxylenol; chloropentostatin; chlorpheniramine and its maleates and tannates; chlorpromazine; cholestyramine resin; choline bitartrate; chondrogenic stimulating protein; cimetidine and its hydrochloride; cinnamedrine hydrochloride; citalopram; citric acid; clarithromycin; clemastine and its fumarate; clonidine and its hydrochloride salt; clorfibrate; cocoa butter; cod liver oil; codeine and its fumarate and phosphate; cortisone acetate; ciprofloxacin HCl; cyanocobalamin; cyclizine hydrochloride; cyproheptadine and its hydrochloride; danthron; dexbromopheniramine maleate;

dextromethorphan and its hydrohalides; diazepam; dibucaine; dichloralphenazone; diclofen and its alkali metal sales; diclofenac sodium; digoxin; dihydroergotamine and its hydrogenates/mesylates; diltiazem; dimethicone; dioxybenzone; diphenhydramine and its citrate; diphenhydramine and its hydrochloride; divalproex and its alkali metal salts; docusate calcium, potassium, and sodium; doxycycline hydrate; doxylamine succinate; dronabinol; efaroxan; enalapril; enoxacin; ergotamine and its tartrate; erythromycin; estropipate; ethinyl estradiol; ephedrine; epinephrine bitartrate; erythropoietin; eucalyptol; famotidine; fenoprofen and its metal salts; ferrous fumarate, gluconate and sulfate; fluoxetine; folic acid; fosphenytoin; 5-fluorouracil (5-FU); fluoxetine and its hydrochloride; furosemide; gabapentan; gentamicin; gemfibrozil; glipizide; glycerine; glyceryl stearate; granisetron and its hydrochloride; griseofulvin; growth hormone; guafenesin; hexylresorcinol; hydrochlorothiazide; hydrocodone and its tartrates; hydrocortisone and its acetate; 8-hydroxyquinoline sulfate; hydroxyzine and its pamoate and hydrochloride salts; ibuprofen; indomethacin; inositol; insulin; iodine; ipecac; iron; isosorbide and its mono- and dinitrates; isoxicam; ketamine; kaolin; ketoprofen; lactic acid; lanolin; lecithin; leuprolide acetate; lidocaine and its hydrochloride salt; lifinopril; liotrix; loratadine; lovastatin; luteinizing hormore; LHRH (lutenizing hormone replacement hormone); magnesium carbonate, hydroxide, salicylate, and trisilicate; meclizine and its hydrochloride; mefenamic acid; meclofenamic acid; meclofenamate sodium; medroxyprogesterone acetate; methenamine mandelate; menthol; meperidine hydrochloride; metaproterenol sulfate; methscopolamine and its nitrates; methsergide and its maleate; methyl nicotinate; methyl salicylate; methyl cellulose; methsuximide; metoclopramide and its halides/hydrates; metronidazole and its hydrochloride; metoprotol tartrate; miconazole nitrate; mineral oil; minoxidil; morphine; naproxen and its alkali metal sodium salts; nifedipine; neomycin sulfate; niacin; niacinamide; nicotine; nicotinamide; nitroglycerine; nonoxynol-9; norethindrone and its acetate; nystatin; octoxynol; octoxynol-9; octyl dimethyl PABA; octyl methoxycinnamate; omega-3 polyunsaturated fatty acids; omeprazole; ondansetron and its hydrochloride; oxolinic acid; oxybenzone; oxtriphylline; para-aminobenzoic acid (PABA); padimate-O; paramethadione;

pentastatin; peppermint oil; pentaerythritol tetranitrate; pentobarbital sodium; perphenazine; phenelzine sulfate; phenindamine and its tartrate; pheniramine maleate; phenobarbital; phenol; phenolphthalein; phenylephrine and its tannates and hydrochlorides; phenylpropanolamine and its hydrochloride salt; phenytoin; pirmenol; piroxicam and its salts; polymicin B sulfate; potassium chloride and nitrate; prazepam; procainamide hydrochloride; procaterol; promethazine and its hydrochloride; propoxyphene and its hydrochloride and napsylate; pramiracetin; pramoxine and its hydrochloride salt; prochlorperazine and its maleate; propanolol and its hydrochloride; promethazine and its hydrochloride; propanolol; pseudoephedrine and its sulfates and hydrochlorides; pyridoxine; pyrolamine and its hydrochlorides and tannates; quinapril; quinidine gluconate and sulfate; quinestrol; ralitoline; ranitadine; resorcinol; riboflavin; salicylic acid; scopolamine; sesame oil; shark liver oil; simethicone; sodium bicarbonate, citrate, and fluoride; sodium monofluorophosphate; sucralfate; sulfanethoxazole; sulfasalazine; sulfur; sumatriptan and its succinate; tacrine and its hydrochloride; theophylline; terfenadine; thiethylperazine and its maleate; timolol and its maleate; thioperidone; trimetrexate; triazolam; tretinoin; tetracycline hydrochloride; tolmetin; tolnaftate; triclosan; trimethobenzamide and its hydrochloride; tripelennamine and its hydrochloride; tripolidine hydrochloride; undecylenic acid; vancomycin; verapamil HCl; vidaribine phosphate; vitamins A, B, C, D, B_1, B_2, B_6, B_{12}, E, and K; witch hazel; xylometazoline hydrochloride; zinc; zinc sulfate; zinc undecylenate. Mixtures and pharmaceutically acceptable salts of these and other actives can be used.

Particularly useful active agents are sparingly soluble solid agents whose dissolution and release properties are enhanced by the solubilizing agents used herein. These agents include H_2 antagonists, analgesics, including non-steroidal anti-inflammatory drugs (NSAIDs), anticholesterolemics, anti-allergy agents and anti-migraine agents.

H_2-antagonists which are contemplated for use in the present invention include cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine and aceroxatidine.

Analgesics include aspirin, acetaminophen, acetaminophen plus caffeine, and

non-steroidal anti-inflammatory drugs (NSAIDS), *e.g.*, aspirin and ibuprofen.

Useful NSAIDs include ibuprofen; diclofenac and its alkali metal salts; fenoprofen and its metal salts; ketoprofen, naproxen and its alkali metal salts; and piroxicam and its salts.

Anticholesterolemics include a wide variety of liquid lowering agents. Among them are bile acid sequestrants, HMG-CoA reductose inhibitors, and statins, *e.g.*, lovastatin, provastatin and the like.

Useful anti-allergy agents include hydricodone and its tartrates; clemastine and its fumarate; azatadine and its maleate; acetaminophen; hydroxyzine and its pamoate and hydrochloride salts; chlorpheniramine and its maleates and tannates; pseudoephedrine and its sulfates and hydrochlorides; bromopheniramine and its maleate; dextromethorphan and its hydrohalides; loratadine; phenylephrine and its tannates and hydrochlorides; methscopolamine and its nitrates; phenylpropanolamine and its hydrochlorides; codeine and its hydrochloride; codeine and its phosphate; terfenadine; acrivastine; astemizole; cetrizine and its hydrochloride; phenindamine and its tartrate; tripelennamine and its hydrochloride; cyproheptadine and its hydrochloride; promethazine and its hydrochloride; and pyrilamine and its hydrochlorides and tannates.

Useful antimigraine agents include divalproex and its alkali metal salts; timolol and its maleate; propanolol and its hydrohalides; ergotamine and its tartrate; caffeine; sumatriptan and its succinate; dihydroergotamine, its hydrogenates/mesylates; methsergide and its maleate; isometheptene mucate; and dichloralphenazone.

Another class of drugs which can be used are antiemetics. Useful antiemetics include: meclizine and its hydrochloride; hydroxyzine and its hydrochloride and pamoate; diphenhydramine and its hydrochloride; prochlorperazine and its maleate; benzquinamide and its hydrochloride; granisetron and its hydrochloride; dronabinol; bismuth subsalicylate; promethazine and its hydrochloride; metoclopramide and its halides/hydrates; chlorpromazine; trimethobenzamide and its hydrochloride; thiethylperazine and its maleate; scopolamine; perphenazine; and ondansetron and its hydrochloride.

Other active ingredients for use in the present invention include antidiarrheals

such as immonium AD, antihistamines, antitussives, decongestants, vitamins, and breath fresheners. Also contemplated for use herein are anxiolytics such as Xanax; antipsychotics such as clozaril and Haldon; antihistamines such as Seldane, Hismanal, Relafen, and Tavist; antiemetics such as Kytril and Cesamet; bronchodilators such as Bentolin, Proventil; antidepressants such as Prozac, Zoloft, and Paxil; antimigranes such as Imigran, ACE-inhibitors such as Vasotec, Capoten and Zestril; Anti-Alzheimers agents such as Nicergoline; and Ca^{II}-Antagonists such as Procardia, Adalat, and Calan.

Combinations of various types of drugs, as well as combinations of individual drugs, are contemplated.

The solubilizing agents, or solubilizers, used herein are commercially available hydrophilic surfactants. One group of useful solubilizers are diblock copolymers containing only polyoxyethylene units and polyoxypropylene units, termed "poloxamers." Poloxamers having polyoxy-ethylene and polyoxypropylene block segments are very useful, and those with about 60% to about 90%, and particularly about 70% to about 80%, polyoxyethylene units are notable. Suitable polymers are sold under "Lutrol", "Monolan" and "Pluronic" trade names (BASF). Poloxamer 188 ("Pluronic F68") is very effective. It contains 80 polyoxyethylene units and 27 polyoxypropylene units, with an average molecular weight of about 7680 to 9510. See Handbook of Pharmaceutical Excipients, 2nd edition, (1994) pages 352-354, which disclosure is hereby incorporated by reference.

Other useful "Pluronic" polymers include those designated as F87, F108, F127 and F237.

Another group of solubilizers are polyethylene glycol esters sold under the "Gelucire" name (Gattefosse). "Gelucire 50/13", a polyethylene glycol-32 glyceryl palmitostearate ester (HLB 13) is useful.

The Process of Making Particulates

Thermoforming techniques useful in making the particulates of the invention include liquiflash and extrusion processing.

Liquiflash Processing

Liquiflash processing involves providing the ingredients at a particle size of less

than 1 μM. Milling/grinding may be necessary preliminary steps. The particles are then blended and used as a feedstock for a suitable device wherein heat and pressure conditions are controlled to effect morphological changes in the feedstock.

Inside the device, the feedstock particles lose their resistance to liquid flow and go into a "liquiform" state. In this state, particles of the material, or a substantial portion thereof, are physically transformed from their original solid state, through a liquid state, and back to a solid state instantaneously. While the particles undergo this transformation, they are acted upon by centrifugal force, or another shearing force, which force separates them into discrete spherical particles, *i.e.*, microspheres. This is termed "spheronization". The transformed particles exit the device as discrete microspheres of about 10 microns to about 600 microns, and generally about 50 to about 300 microns particle diameter.

U. S. Patents 5,445,769 and 5,458,823, and application Serial Nos. 08/330,412 and 08/874,215, set out the details of the liquiflash and flash flow spheronization processes. Their disclosures are incorporated herein by reference.

Extrusion Processing

Extrusion techniques to be used in the invention include those in which the temperatures range from those at or below which a drug/solubilizer eutectics form to those at or below which the active ingredient(s) melt or readily dissolve in the solubilizer(s). One exemplary technique employs ibuprofen/Pluronic F68 combinations and temperatures of about 35°C to about 45°C.

Extruders, flash flow spinning heads, and the like are useful devices.

The particulates may be ground or reduced in size by other means.

Dosage Forms

The particulates can be used as is, e.g., in powders, sachets and the like, or as ingredients in other dosage forms, such as caplets, capsules, and tablets. Such dosage forms can contain the microspheres or other particulates described herein and one or more conventional pharmaceutical additives.

The microspheres are optionally coated with suitable amounts of one or more pharmaceutical coatings. Conventional coatings include taste-masking coatings, enteric

coatings and the like. The coatings may not significantly alter the dissolution and release properties of the product. Cellulosic coatings, in sutiable amounts, are contemplated. Suitable amounts and types of excipients, *e.g.*, fillers, flavors, flow control agents, lubricants, perfumes, can be blended with the microspheres before or during preparation of a final dosage form.

When the microspheres are used to make tablets, the concentrations of tablet ingredients will fall into the ranges shown in Table 1.

Table 1. Tablet Ingredients

INGREDIENT	BROAD RANGE (%)	NARROW RANGE (%)
PARTICULATES	50 - 70	55 - 60
SOLID DILUENT(S)	20 - 40	30 - 35
DISINTEGRANT(S)	3 - 5	3 - 4
GLIDANT(S)	2 - 5	2 - 3
LUBRICANT(S)	2 - 5	2 - 3
OTHER ADDITIVES	0 - 10	0 - 5

The solid diluent is generally a bulking agent. It is typically present a weight concentration which is 1/2 to 2/3 of the concentration of microspheres.

Useful solid diluents are microcrystalline cellulose products having mean particle sizes of about 20 microns to about 180 microns. The Avicel products, especially Avicel PH101 (FMC) are effective.

Disintegrants may assist in the release of the active agent after ingestion of the dosage form. Useful disinte-grants include croscarmellose sodium, polyvinylpyrrolidone (PVP), sodium starch glycolate and mixtures thereof. "Act-Di-Sol", a croscarmellose sodium product made by FMC, is very useful, as is Kollidon CL-M, a crospovidone (BASF).

One or more glidants such as starch, talc, lactose, stearates and colloidal silica

can be used. "Cab-o-sil M5", a brand of colloidal silica made by Cabot, is very useful.

Lubricants are used in the tablet compositions, among them stearic acid and its esters, adipic acid, fatty acid esters, talc, magnesium stearate, mineral oil and the like and mixtures thereof. Magnesium stearate is highly effective.

Other conventional pharmaceutical additives and coatings can be employed.

Mixing Procedures

The microspheres are mixed with the other tablet composition ingredients using conventional equipment.

Tablets were made on a rotary tablet press, such as a Stokes or Kilian rotary tablet press.

Examples

The following examples illustrate the invention:

Example I

Lovastatin Microspheres

Lovastatin powder and milled Polaxamer 188 in a ratio of 5:95 were placed in a Stephan mixer in the following order: (1) one-half of the solubilizing agent, (2) all of the lovastatin, (3) the remaining portion of the solubilizing agent. The ingredients were mixed for about five minutes and used as a feedstock, as follows:

The feedstock was fed to the 5-inch spinning head disclosed in U. S. Application Serial No. 08/874,215, filed June 13, 1997. The head speed was increased to 60Hz while the heating elements were raised to a temperature which produced liquiflash conditions (about 60°C to 90°C).

The spinning head forced the material through the screen and the product was permitted to free fall a distance of from six to eight feet below the head. The product consists of binary microspheres containing lovastatin and a solubilizer and having a

highly consistent particle size, with diameters of about 100 microns to about 400 microns.

Example II

Lovastatin Microspheres

Using a procedure similar to that used in Example I, microspheres containing 20:80 and 40:60 lovastatin:solubilizing agent were prepared. Poloxamer 188 was used.

Example III

Lovastatin Dissolution Studies

The 40:60 lovastatin:solubilizer microspheres were tested using the standard *in vitro* dissolution test procedure of USP App. II at 50 rpm, 900 mL dissolution buffer, pH 7.0 with 2% sodium lauryl sulfate, with the following dissolution profile:

Table 2a. Dissolution of Lovastatin Microspheres

TIME (MINUTES)	PERCENT DISSOLVED
5	88
10	98
20	100
30	101*
45	101*
60	101*

*theoretical

For comparison, a dissolution study was run on 20 mg tablets of "Mevacor," a commercial lovastatin preparation (Merck). This product contains lovastatin, cellulose, lactose, magnesium stearate, starch and butylated hydroxyanisole. See Physician's

Desk Reference, 51st ed. (1997), p. 1742, incorporated herein by reference.

Using the test procedure described above, the "Mevacor" tablets exhibited the following dissolution profile:

Table 2b. Dissolution of Commercial Tablets

TIME (MINUTES)	PERCENT DISSOLVED
5	30
10	66
20	86
30	90
45	92

Clearly, the microspheres of the invention dissolved faster than the commercial formulation. Eighty-eight percent (88%), 98%, and 100% of the lovastatin in the microspheres dissolved in 5 minutes, 10 minutes, and 20 minutes, respectively, compared to 30%, 66%, and 86% dissolution for the commercial product at the same time points.

Table 3. Lovastastin Aqueous Solubility

PRODUCT	AQUEOUS SOLUBILITY (ug/mL)
RAW DRUG MATERIAL	3.94
5/95 LOVASTATIN/PLURONIC F68	15.43
10/90 LOVASTATIN/PLURONIC F68	16.43
20/80 LOVASTATIN/PLURONIC F68	18.47

These values were derived by placing a 100 mg drug equivalent sample in 100 mL water in a beaker and stirring overnight. The solution made is tested by HPLC to determine the concentration of drug therein.

Example IV

Lovastatin Bioavailability Study

In *in vitro* bioavailability tests, gelatin capsules containing microspheres made using the invention gave superior plasma profiles to those obtained using the commercial lovastatin tablet. The study protocol was designed to determine mevinolinic acid concentrations in blood samples taken at various points in time. Mevinolinic acid is a metabolite associated with lovastatin use.

Abstract of Bioavailability Protocol

Name of Samples:	Immediate-release lovastatin and Mevacor®
Active Ingredients:	Lovastatin USP
Study Dosage:	4x20mg tablets, Mevacor (Merck & Co.) Immediate-Release Lovastatin 4x20mg capsules, 20:80 Lovastatin:Pluronic.
Objective:	Determine the single-dose bioavailability of an investigational formulation of immediate-release lovastatin relative to Mevacor®
Population:	Healthy, nonsmoking male and female human volunteers, 40 to 70 years of age, inclusive.
Study Design:	Single center, randomized, open label, 3-way crossover design - 3 treatments, 3 periods lasting approximately 3 days each; minimum 7-day washout.
Sample Size:	9 subjects.
Sample Analysis:	Serum mevinolinic acid.
Primary Variables:	Serum mevinolinic acid C_{max}, T_{max} and AUC_0.
Blood Samples:	Pre-dose and 0.5, 1, 1,5, 2, 3, 4, 5, 6, 8, 10, 12, and 24 hours after dosing.

The results are shown in the following table:

Table 4. Plasma Concentrations of Mevinolinic Acid over Time

HOURS	MEVOLINIC ACID (ng/mL)	
	MEVACOR LOW - HIGH	LOVASTATIN LOW - HIGH
0.0	0.00 - 0.00	0.00 - 0.00
0.5	0.1 - 0.963	0.00 - 0.00
1	0.185 - 11.6	0.00 - 0.979
1.5	0.277 - 19.3	0.00 - 6.26
2	0.729 - 24.6	0.287 - 5.96
3	0.508 - 29.4	1.83 - 32.8
4	0.820 - 27.7	2.26 - 36.6
5	0.845 - 21.2	2.33 - 36.8
6	1.31 - 14.7	1.57 - 33.6
8	1.43 - 9.80	1.27 - 19.6
10	0.749 - 9.09	0.918 - 17.2
12	0.350 - 4.99	0.443 - 8.31
18	0.158 - 3.51	0.146 - 8.32
24	0.113 - 2.38	0.128 - 5.67

Table 5. Pharmacokinetic Parameters

PARAMETERS	MEVACOR MEAN (SD)	LOVASTATIN MEAN (SD)
C_{MAX} (ng/mL)	9.89 (8.13)	12.7 (10.1)
T_{MAX} (hr)	4.60 (2.3)	5.1 (0.78)
A.U.C. (0-last)*	72.6 (60.8)	92.9 (97.4)
A.U.C. (0-inf)*	82.0 (71.4)	118 (153)

*expressed as ng/hr/mL

Reasonable variations, such as those which would occur to a skilled artisan, can be made herein without departing from the scope of the invention.

WE CLAIM:

1. Microspheres useful in making dosage forms having improved dissolution and bioavailability consisting essentially of:

(a)from about 5% to about 80% by weight of one or more active ingredients, and

(b)from about 95% to about 20% by weight of one or more solubilizing agents.

2. The microspheres of claim 1 wherein (b) is at least one diblock copolymer containing polyoxyethylene and polyoxypropylene units.

3. The microspheres of claim 2 wherein the (a)contains at least one active agent selected from the group consisting of: analgesics, H_2- antagonists, non-steroidal anti-inflammatory drugs (NSAIDs), anticholesterolemics, anti-allergy agents, and anti-migraine agents.

4. The microspheres of claim 1 wherein the active agent is lovastatin.

5. A dosage unit comprising the microspheres of claim 1, and one or more pharmaceutical excipients.

6. The dosage unit of claim 5 wherein (b) is a diblock copolymer containing polyoxyethylene and polyoxypropylene units.

7. The dosage unit of claim 6 wherein (a) contains at least one active agent selected from the group consisting of: analgesics, H_2- antagonists, non-steroidal anti-inflammatory drugs (NSAIDs), anticholesterolemics, anti-allergy agents, and anti-migraine agents.

8. The dosage unit of claim 7 wherein (a) is lovastatin.

9. The dosage unit of claim claim 8 having improved dissolution and bioavailablity.

10. A process for improving the dissolution and bioavailability of an active agent comprising delivering that agent via the dosage unit of claim 5.

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/US 98/19735

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/16 A61K47/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 23700 A (UNIV GENT ;REMON JEAN PAUL (BE)) 27 October 1994 see page 4, line 35 - page 5, line 5 see page 5, line 10 - page 6, line 21 see claims 1-7	1-3,5-7, 10
X	WO 96 39835 A (EMISPHERE TECH INC ;KANTOR MARTIN L (US)) 19 December 1996 see page 18; claims 10,11; example 3	1,5,10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

Information on patent family members

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PCT/US 98/19735

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